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(54) Title: PRESSURISED AEROSOL COMPOSITIONS

(57) Abstract

A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

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Pressurised Aerosol Compositions

This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquefied chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all applications of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

The use of hydrofluorocarbons as aerosol propellants has also been suggested. However, considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofluoroalkanes and capable of stabilising medicament suspensions.

Surprisingly, we have found that certain polymers are both soluble in the aerosol propellants and capable of stabilising medicament compositions.

Thus, according to the invention, we provide a pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

The polymer may be a homopolymer, that is the polymer consists of the same recurring structural units, or it may be a copolymer, that is the polymer contains recurring units in addition to either amide containing units or carboxylic acid ester units. The polymer may also be a copolymer of amide containing units and

carboxylic acid ester units. Such copolymers may be either block copolymers or random copolymers.

We preter polymers which include recurring structural units containing an amide group. We particularly prefer the amide containing unit to be 1-ethylene-pyrrolidin-2-one. We especially prefer the polymer to be a homopolymer containing recurring 1-ethylene-pyrrolidin-2-one, that is polyvinylpyrrolidone.

In general, we have found that polyvinylpyrrolidones having a wide range of average molecular weights give acceptable suspensions. Although polymers can be characterised by their weight average molecular weights, viscosity average molecular weights or number average molecular weights, it is more usual to characterise polymers, in particular polymers such as polyvinylpyrrolidone, by K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, 13, 58-64 and 71-74). In particular we prefer the polymer to have a K value of from 10 to 150, more preferably 15 to 120. Particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125.

Suitable polymers containing carboxylic acid ester containing recurring structural units include polyvinylacetate and copolymers of vinyl acetate and vinyl pyrrolidone, that is polyvinylpyrrolidone/vinyl acetate copolymer. We have found that polyvinylacetate with a weight average molecular weight of 250,000 gives particularly stable suspensions.

Other polymers that may be mentioned include acrylic acid/methacrylic acid ester copolymers, especially those in which the methyl and ethyl ester groups have been replaced with a low content of trimethylammoniumethyl groups, preferably at a ratio of 1:20, especially at a ratio of 1:40. We have found that such copolymers having a weight average molecular weight of 150,000 give stable suspensions.

The amount of polymer in the composition will depend on the active ingredient to be dispersed, its concentration and the particular polymer selected. However, in general the amount of polymer is from 0.00001 to 10% w/w, more preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w.

The compositions may, in addition to the polymer, contain other excipients, in particular excipients intended to improve valve lubrication and excipients to modify flavour. Particular lubricants that may be mentioned include polyethoxylated

compounds, especially polyethylene glycol. We prefer polyethylene glycol having a mean molecular weight of from 200 to 3000, preferably 400 to 2000, eg 1500. Other polyethoxylated compounds that may be used as lubricants include polysorbates, eg polysorbate 80, and alkyl aryl polyether alcohols, eg tyloxapol. Other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofluorocarbons and esters of medium chain fatty acids. The amount of lubricant in the composition will depend on the other components of the composition, the active ingredient, the nature of the valve, etc. In general, we prefer a concentration of 0.01 to 4% w/w and more preferably 0.1 to 2% w/w.

Flavour modifying excipients that may be added to the composition include peppermint oil, menthol, Dentomint (Dentomint is a tradename), saccharin and saccharin sodium. When the flavour modifying excipient is a solid, preferably it is micronised. The concentration will depend on the individual composition and the flavour modifying excipient. In general, we prefer a concentration of 0.005 to 4% w/w; more preferably 0.01 to 1% w/w.

By the term 'hydrofluoroalkane' we mean a compound of general formula

$$C_xH_yF_z$$

in which x is an integer from 1 to 3, y+z=2x+2 and y and z are both at least 1.

Particular hydrofluoroalkanes of interest are CF_3CFH_2 (Propellant 134a), CH_3CHF_2 (Propellant 152a) and CF_3CHFCF_3 (Propellant 227). We particularly prefer compositions including propellant 227.

In general the vapour pressure of the propellant mixture should be in the range suitable and permitted for aerosol propellants. The vapour pressure may be varied by mixing one or more hydrofluoroalkanes and/or some other suitable vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psig, more preferably 40 to 80 psig, eg about 60 psig.

In certain cases we have found it advantageous to add to the compositions excipients capable of increasing the solubility of the polymer or of other excipients, in the propellant. In general we have found that the polymers selected have a solubility in the propellant of at least 0.0001% w/w, preferably at least 0.001% w/w, particularly 0.01% w/w and especially 0.1% w/w. Excipients capable of increasing the solubility of the polymer include liquid excipients which are more polar than the liquefied

propellant, where polarity is defined in terms of relative Kauri butanol values, as described in European patent application 0 372 777. Particular excipients that may be mentioned include alcohols eg ethanol and isopropanol. However, in contrast to the teaching of EP 0 372 777, we have found that only very small quantities of such excipients are required. In particular we have found that good compositions can be prepared in propellant 134a with polyvinylpyrrolidone as polymer with a variety of active ingredients and less than 10% w/w, preferably less than 5% w/w, more preferably less than 2% w/w, eg 0.2% w/w ethanol.

Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments which are conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone propionate, budesonide and tipredane, and bronchodilators, eg salbutamol, reproterol, terbutaline, formoterol, pirbuterol, isoprenaline, salmeterol, fenoterol and salts thereof, and anticholinergic agents such as ipratropium bromide, oxitropium bromide and atropine and combinations of two or more of these agents, eg a combination of a prophylactic agent with a bronchodilator, eg sodium cromoglycate with salbutamol.

Other medicaments that may be mentioned include antihistamines, eg clemastine, pentamidine and salts thereof, acetyl-β-methylcholine bromide, peptide hormones such as insulin and amylin, bradykinin antagonists, PLA_2 inhibitors, PAF antagonists, lipoxygenase inhibitors, leukotriene antagonists, CNS active drugs, such as NMDA antagonists, glutamate antagonists, CCK agonists and antagonists; macrolide compounds including FK 506, rapamycin, cyclosporin and structurally related compounds, vitamins, vaccines, eg MMR vaccine and polio vaccine and vectors for gene therapy, eg plasmids containing genes intended to correct genetic disorders such as cystic fibrosis.

Where the medicament is intended for delivery to the lung, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the medicament is

preferably in a form having a mass median diameter of from 0.01 to 10 μm, more preferably from 0.1 to 4 μm, eg about 2 or 3 μm.

The amount of medicament in the composition will depend on the nature of the active ingredient and the condition to be treated. However, the composition preferably comprises from 0.01 to 15% w/w, preferably from 0.1 to 10% w/w, and most preferably from 0.5 to 5% w/w medicament.

According to a further aspect of the invention there is provided a method of producing a pressurised aerosol composition as herein described, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

In particular, the compositions may be produced by cold fill or pressure fill techniques. In cold filling, the ingredients are placed in a cooled mixing vessel, cooled liquefied propellant added and a dispersion produced by vigorous stirring. Alternatively, a slurry may be prepared of the ingredients in a portion of cooled liquid propellant and the remainder of the liquefied propellant added under vigorous stirring. Aliquots of the dispersed composition are then filled into cooled aerosol cans and sealed with a suitable valve, eg a metering valve.

In pressure filling, the ingredients are placed in a pressure vessel, liquefied propellant added under pressure through a valve and a dispersion of the ingredients in the liquefied dispersed composition are then filled, under pressure, through the valve into suitable cans provided with appropriate valves, eg metering valves.

The compositions according to the invention are advantageous in that the solubility of the polymer is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve.

The compositions of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

The performance of the compositions according to the present invention can be assessed using the following test procedures:

1. Settling times

A glass bottle containing the composition is gently shaken five times and then stood upright. The time interval between standing the bottle upright and the first appearance of flocculation or separation of powder in the propellant determined (S_1). Timing is continued until complete separation, defined as when three lines of standard newspaper print can be read through the propellant from the top or bottom, depending on whether the active ingredient floats or sinks (S_2). In some compositions, complete separation does not occur. For these compositions, a turbidity factor ranging from 1 to 5 is determined, 1 denoting that a small proportion of the active ingredient is suspended and 5 denoting that the majority of the active ingredient is suspended.

2. Dispersion Tests

Dispersion testing on compositions formulated in cans having a metering valve can be assessed using a glass multistage liquid impinger, eg of the type described by J.H. Bell *et al*, *J. Pharm. Sci.*, 1971, 60(10), 1559.

3. Lubrication

The lubricating effects of the composition can be assessed by filling the formulation into a can and closing the can with a modified metering valve from which the return spring has been removed. The stem of the valve is subjected to a compression force and the reading recorded in Newtons. This gives a measure of the lubricating efficacy of the composition.

4. Dose uniformity

Dose uniformity is assessed by discharging a metered dose aerosol can containing the composition into a filter tube which has sufficient air flowing through it to entrain all the dose. The tube is washed out with a suitable solvent and the amount of medicament assayed. The medicament entrained on the mouthpiece is also washed off and assayed. The variation of dose evaluated throughout the life of the can is a measure of dose uniformity. In a variation of this test, dose uniformity after standing can be assessed by shaking the aerosol can, allowing to stand for a predetermined time and assessing dose in the manner described above.

5. Caking potential

Compositions to be assessed are filled into plastic coated glass bottles. The assessment is carried out by allowing the samples to be stored for a period of time in

order that complete sedimentation and compaction of the powder mass can take place, eg 3 months. After that period, the glass bottles are shaken by gentle twisting of the hand to totally invert the bottles. The number of bottle inversions required to completely resuspend the drug is noted. The number gives a measure of the degree of compaction of the composition. Since ease of drug particle redispersion is essential for dose uniformity, any composition requiring more than 5 shakes suggests possible problems in long-term storage.

The invention will now be illustrated, but in no way limited, by the following Examples.

Examples

Method

The required amounts of micronised active ingredient, suspending agent and other excipients, were weighed into plastic coated glass bottles and crimped with an appropriate valve. The desired amount of liquefied propellant was then transferred using a transfer button and the contents of the bottle sonicated to ensure thorough mixing. Unless otherwise stated, the fill volume for the bottles was 20 ml.

Materials

Active ingredients

All active ingredients were micronised. In general, the active ingredients were anhydrous, although nedocromil sodium and sodium cromoglycate were used in their equilibrium hydrated form which each contain about 10% w/w water at room temperature.

Polyethyleneglycols (PEG)

The average molecular weight of the polyethyleneglycol used is indicated by the number 200, 400, etc following PEG.

Halocarbon oil

Halocarbon oil is the proprietary name given to a series of high molecular weight fully halogenated chlorofluorocarbons of chlorotrifluoroethylene telomers obtainable from Halocarbon Products Corporation, New Jersey, USA.

Miglyols

Miglyol® neutral oils

Miglyol® neutral oils are esters of medium chain fatty acids and are sometimes referred to as fractionated coconut oils. Miglyol is a trademark of Hüls AG. The following oils were used.

Miglyol® 810

A triglyceride of fractionated C_8/C_{10} coconut oil fatty acids classified by the CTFA as caprylic/capric triglyceride. It meets the requirements of the British Pharmacopoeia 1988 for the monograph "Fractionated Coconut Oil". It is a low viscosity oil of neutral taste and smell, with a turbidity point below 0°C.

Miglyol® 829

A glyceryl ester of fractionated C_8/C_{10} coconut fatty acids linked to succinic acid and is classified by the CTFA as caprylic/capric/diglyceryl succinate. It has a turbidity point below -30°C, is soluble in alcohol, has a viscosity of approximately 250 mPa.s and a density of approximately 1.

Miglyol® 840

A propylene glycol diester of saturated vegetable fatty acids with C_8/C_{10} chain lengths, classified by the CFTA as propyleneglycol dicaprylate/dicaprate. It meets the requirements of the German Pharmacopoeia, DAR9, 1st supplement, for the monograph "Propyleneglycoloctanoatodecanoate". It has a turbidity point below -30°C and is soluble in 90% ethanol.

Polyvinylpyrrolidones

All polyvinylpyrrolidones used were essentially linear homopolymers formed by the free radical polymerisation of N-vinylpyrrolidone. PVP(K29/32), PVP(K90), PVP(K120), PVP(C15) and PVP(C30) refer to the polyvinylpyrrolidones obtainable from GAF Chemical Corporation and sold under the Trade Mark PLASDONE®. PVP/17PF refers to KOLLIDON 17PF, a polyvinylpyrrolidone available from BASF (KOLLIDON is a registered Trade Mark).

The manufacturing processes for polyvinylpyrrolidone and the other polymers used herein produce polymer mixtures containing molecules of unequal chain length and thus different molecular weights. Such polymers are usually characterised by their K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, 13, 58-64 and 71-74). The polymers can also be characterised by their average molecular weights ($\bar{M}w$),

viscosity average molecular weights ($\overline{M}v$) and number average molecular weights ($\overline{M}n$).

Characterising data for the polyvinylpyrrolidones used were as follows:

	K	$\overline{M}w$	$\overline{M}v$	$\overline{M}n$
PVP 17 PF	15-18	9000	-	2500
K29/32	29-32	-	-	-
K90	94±6	1,280,000	63000	-
K120	120±5	2,800,000	1,450,000	-
C15	17±1	10500	7000	3000
C30	30.5±1	62500	3800	16500

Polyvinylpyrrolidone/vinylacetate copolymers

Polyvinylpyrrolidone/vinylacetate copolymers are obtainable from GAF Chemical Corporation. The E- and I- series of PVP/VA copolymers were supplied as 50% solutions in ethanol and isopropanol respectively. S-630 refers to the white, spray dried polymer of PVP/VA having the characteristics set out below.

Characterising data for PVP/VA used:

		K value	VP/VA ratio
PVP/VA	S-630	30-50	60/40
	E-535	30-50	50/50
	I-535	25-35	50/50
	E-335	25-35	30/70

Acrylic acid/methacrylic acid ester copolymers

The acrylic acid/methacrylic acid ester copolymers used were copolymers synthesized from acrylic and methacrylic acid ethyl and methyl esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the neutral (meth)acrylic acid esters is 1:40. The weight average molecular weight is approximately 150000. The polymer used was EUDRAGIT RS PM, obtainable from Röhn Pharma GmbH. (EUDRAGIT is a registered Trade Mark).

Polyvinylacetate

The polyvinylacetate used had a weight average molecular weight of about 26,000.

A. **Compositions containing polyvinylpyrrolidone and propellant 227**

The following active ingredients were formulated at the concentration shown with PVP in propellant 227 PLASDONE C30 (PLASDONE is a registered Trade Mark of GAF Chemicals Corporation).

a) with 0.05% w/w PVP(C-30)

1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml
6.	Fenoterol hydrobromide	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Sodium cromoglycate	50mg/ml
9.	Ipratropium bromide	0.8mg/ml
10.	Pentamidine isoethionate	4mg/ml
11.	Clemastine	4mg/ml
12.	Acetyl-β-methylcholine bromide	10mg/ml
13.	Budesonide	4mg/ml

b) with 0.1% w/v PVP(17PF)

1.	Fenoterol hydrobromide	4mg/ml
2.	Terbutaline sulphate	5mg/ml
3.	Salbutamol sulphate	4mg/ml

c) with 0.025% w/v PVP(C30)

1.	Tipredane	10mg/ml

B. Compositions containing polyvinylpyrrolidone/vinyl acetate copolymer in propellant 227

The following active ingredients were formulated in propellant 227 at the concentrations shown.

a) with 0.05% w/v PVP/VA S-630

1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml

6.	Fenoterol hydrobromide	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Sodium cromoglycate	50mg/ml
9.	Ipratropium bromide	0.8mg/ml
10.	Acetyl-β-methylcholine bromide	10mg/ml
11.	Budesonide	4mg/ml

b) with 0.025% w/v PVP/VA S-630

1.	Tipredane	10mg/ml

C. **Compositions containing PVP or PVP/VA, propellant 227 and polyethylene glycol**

The following active ingredients were formulated in propellant 227 at the concentration shown with 0.5% w/v PEG600.

a) with 0.05% w/v PVP(C30)

1.	Salbutamol sulphate	4mg/ml
2.	Sodium cromoglycate	50mg/ml
3.	Reproterol hydrochloride	10mg/ml

b) with 0.05% w/v PVP/VA S-630

1.	Salbutamol sulphate	4mg/ml
2.	Sodium cromoglycate	50mg/ml
3.	Reproterol hydrochloride	10mg/ml
4.	Budesonide	4mg/ml

c) with 0.1% w/v PVP(17PF)

1.	Terbutaline sulphate	5mg/ml
2.	Fenoterol hydrobromide	4mg/ml

D. **Compositions containing acrylic acid/methacrylic acid ester copolymers and propellant 227**

The following active ingredients were formulated at the concentration shown with 0.1% w/v EUDRAGIT RS (EUDRAGIT is a Trade Mark of Röhn Pharma GmbH) in propellant 227.

a)

1.	Terbutaline	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone	4mg/ml

5.	Reproterol hydrochloride	10mg/ml
6.	Fenoterol	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Ipratropium bromide	0.8mg/ml
9.	Clemastine	4mg/ml
10.	Acetyl-β-methylcholine bromide	10mg/ml

b) compositions including 0.5%w/w PEG 600

11.	Beclomethasone dipropionate	5mg/ml
12.	Sodium cromoglycate	50mg/ml
13.	Reproterol hydrochloride	10mg/ml
14.	Fenoterol hydrobromide	4mg/ml

E. Compositions in propellant 134a

The following active ingredients were formulated at the concentration shown in propellant 134a.

1.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	5.0% w/w
2.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
3.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1%/ w/w
	ethanol	5.0% w/w
4.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
5.	Tipredane	10mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
6.	Tipredane	10mg/ml
	PVP(C30)	0.25% w/w
	ethanol	5.0% w/w
7.	Tipredane	10mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w

8.	Nedocromil sodium	20mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
9.	Nedocromil sodium	20mg/ml
	PVP/C30	0.25% w/w
	ethanol	5.0% w/w
10.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w
11.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
12.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
13.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
14.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
15.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.05% w/w
	PEG 600	0.5% w/w
	ethanol	0.2% w/w
16.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	2.0% w/w
17.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
18.	Beclomethasone	

dipropionate	5mg/ml
PVP(C30)	0.1% w/w
ethanol	5.0% w/w

F. Compositions containing polyvinylacetate

a) in propellant 134a

1.	Tipredane	10mg/ml
	Polyvinylacetate	0.042% w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.042% w/w

b) in propellant 227

1.	Tipredane	10mg/ml
	Polyvinylacetate	0.035% w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.035% w/w

G. Compositions using polyvinylpyrrolidone of different K values

The following active ingredients were formulated in propellant 227 at the concentrations shown, with 0.1% w/w polyvinylpyrrolidone having the K value shown:

a) PVP(K29/32)

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml
3.	Sodium cromoglycate	20mg/ml
4.	Reproterol hydrochloride	4mg/ml
5.	Salbutamol sulphate	4mg/ml

b) PVP(K90)

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

c) PVP(K120)

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

d) PVP(C15)

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

H. Compositions using polyvinylpyrrolidone/vinylacetate

copolymers of different vinylpyrrolidone/vinylacetate ratios

Tipredane and nedocromil sodium were formulated in propellant 227 at the concentrations shown, with 0.1% w/w PVP/VA having the vinylpyrrolidone/vinylacetate ratio shown.

a) Nedocromil sodium 20mg/ml

1. PVP/VA E-535 (50/50)
2. PVP/VA I-535 (50/50)
3. PVP/VA E-335 (30/70)

b) Tipredane 10mg/ml

1. PVP/VA E-535 (50/50)
2. PVP/VA I-535 (50/50)
3. PVP/VA E-335 (30/70)

I. Further tipredane formulations

Ex	Tipredane (mg/ml)	PVP/VA S-630 % w/w	PVP/C30 % w/w	Propellant
1	4	0.0025	-	134a
2	4	0.01	-	134a
3	4	0.025	-	134a
4	4	0.05	-	134a
5	10	0.0025	-	134a
6	10	0.01	-	134a
7	10	0.025	-	134a
8	10	0.05	-	134a
9	30	0.0025	-	134a
10	30	0.01	-	134a
11	30	0.025	-	134a
12	30	0.05	-	134a
13	4	0.0025	-	227
14	4	0.01	-	227
15	4	0.025	-	227
16	4	0.05	-	227
17	10	0.0025	-	227
18	10	0.01	-	227
19	10	0.025	-	227
20	10	0.05	-	227
21	30	0.0025	-	227
22	30	0.01	-	227
23	30	0.025	-	227
24	30	0.05	-	227
25	4	-	0.0025	134a

26	4	-	0.01	134a
27	4	-	0.025	134a
28	4	-	0.05	134a
29	10	-	0.0025	134a
30	10	-	0.01	134a
31	10	-	0.025	134a
32	10	-	0.05	134a
33	30	-	0.0025	134a
34	30	-	0.01	134a
35	30	-	0.025	134a
36	30	-	0.05	134a
37	4	-	0.0025	227
38	4	-	0.01	227
39	4	-	0.025	227
40	4	-	0.05	227
41	10	-	0.0025	227
42	10	-	0.01	227
43	10	-	0.025	227
44	10	-	0.05	227
45	30	-	0.0025	227
46	30	-	0.01	227
47	30	-	0.025	227
48	30	-	0.05	227

J. **Compositions containing flavouring agents**

The following compositions were made up in propellant 227, with 0.1% w/w PVP/VA S-630.

1.	Nedocromil sodium	20mg/ml
	peppermint oil	0.1% w/w
2.	Nedocromil sodium	20mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w
3.	Tipredane	10mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w

K. **Compositions containing additional excipients**

The following composition was made up in propellant 227, to examine the effects of different excipients as valve lubricants.

a)	Nedocromil sodium	20mg/ml
	PVP/C30	0.1% w/w

	Lubricant		0.5% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
	Lubricants:		
	PEG 200		
	PEG 400		
	PEG 600		
	PEG 1000		
	Miglyol 810		
	Miglyol 829		
	Miglyol 840		
	Ethyl oleate		
	Halocarbon oil 27		
	Tyloxapol		
	Polysorbate 80		
b)	Nedocromil sodium		20mg/ml
	PVP (C30)		0.10% w/w
	PEG 1500		0.20% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
c)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.50% w/w
	Lubricants:	PEG 600	
		PEG 1000	
d)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.20% w/w
	Lubricants:	PEG 600	
		PEG 1000	
		PEG 1500	

Claims

1. A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

2. A composition according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.

3. A composition according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.

4. A composition according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.

5. A composition according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.

6. A composition according to any one of Claims 1 to 3 or Claim 5, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.

7. A composition according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.

8. A composition according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.

9. A composition according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, clemastine, acetyl-β-methylcholine bromide and budesonide.

10. A process for the preparation of a composition according to Claim 1, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

INTERNATIONAL SEARCH REPORT

PCT/GB 92/01749

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K9/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0 372 777 (RIKER LABORATORIES INC.) 13 June 1990 cited in the application see claims 1,12	1-10
Y	WO,A,8 705 211 (BURGHART KURT) 11 September 1987 see the whole document	1-10

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 OCTOBER 1992	20. 11. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201749 SA 64798

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0372777	13-06-90	AU-A-	4595689	14-06-90
		CA-A-	2004598	06-06-90
		EP-A-	0499344	19-08-92
		JP-A-	2200627	08-08-90
WO-A-8705211	11-09-87	AU-B-	597049	24-05-90
		AU-A-	7127987	28-09-87
		CA-A-	1293929	07-01-92
		DE-A-	3775960	27-02-92
		EP-A,B	0240484	07-10-87
		JP-T-	63503304	02-12-88
		US-A-	4869899	26-09-89
		ZA-A-	8701721	31-08-87